

Original Research Article

Clinical outcome after surgical resection of small bowel cancer

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ABSTRACT

Background: Small bowel cancer (SBC) is rare, however there is recent trend toward increased incidence.

Methods: Retrospective evaluation of the clinical presentation, diagnosis, management and clinical outcome of adult patients with primary SBC who were admitted at Sohag University Hospital during 2014-2019.

Results: Twenty-one patients with SBC were enrolled (14 males and 7 females) with median age of 56 (range 32-83) years. Small bowel mass was identified preoperatively in 13 patients (62%). Thirteen patients (62%) presented with abdominal emergencies after failure of prompt diagnosis of non-specific abdominal pain of variable durations (median: 4, range: 2-11 weeks). Apart from duodenal tumors, histopathological diagnosis for jejunal and ileal tumors was not achieved preoperatively. Tumor types were gastrointestinal stromal tumors, GISTs (9, 43%), lymphoma (8, 38%) and adenocarcinoma (4, 19%). Patients with jejunal and ileal masses were managed by resection and primary anastomosis. Duodenal tumors required local resection in 2 and pancreatico-duodenectomy in 4 patients. Increased risk of aggressive behavior in GISTs, advanced stage and incomplete resection in lymphomas and adenocarcinomas were associated with higher recurrence rates and diminished survival. Follow-up ranged from 5 to 48 months, with survival rate of 76% (16 patients alive).

Conclusions: The diagnosis of SBC is difficult and delayed. Appropriate surgical management, even during emergency, could achieve prolonged survival.

Keywords: Small bowel cancer, GIST, Duodenal tumors

INTRODUCTION

Small bowel cancer (SBC) is uncommon disease, representing only 0.6% of all cancers and less than 5% of malignant tumors of the digestive system.^{1,2} The small bowel comprises about 75% of the length of the digestive tract and 90% of its mucosal surface.³ Theoretically, the disparity between the very large mucosal surface of small bowel and incidence of SBC could be attributed to the limited transit time in the course of the small bowel and subsequent reduction of contact between the intestinal mucosa and nutritional carcinogen.⁴ Furthermore, the lesser microbiota concentrations may contribute to diminution of synthesis of the carcinogenic deoxycholic acid from bile salts.^{4,5} Histopathologically, more than 40 neoplastic varieties involving the small bowel were reported, however only 4 types constitute more than 95%

of SBC, including adenocarcinoma, gastrointestinal stromal tumors (GISTs), carcinoids or lymphomas.^{6,7} Non-modifiable risk factors include hereditary mutations like those with familial adenomatous polyposis, Lynch syndrome, multiple endocrine neoplasia syndrome type I and Peutz-Jeghers syndrome, inflammatory bowel and celiac disease.⁴ Modifiable risk factors comprise smoking, heavy consumption of alcohol and dietary animal fat and protein, obesity, gall stones and vitamin D deficiency.⁸ SBC presents with vague symptoms such as colicky abdominal pain, vomiting, weight loss and small bowel obstruction with average period of delay between the onset of symptoms and diagnosis of approximately 30 weeks.⁹ The introduction of modern diagnostic tools, like capsule endoscopy and computed tomography protocols designed for small intestinal imaging, enabled detection of SBC at early stages.¹⁰ However, over 50% of symptomatic

patients are diagnosed with metastasis or during exploratory laparotomy.^{4,9} Prognosis of SBC is strongly related to the stage of the disease. Poor prognostic factors include male gender, low albumin, high levels of tumor markers (carcinoembryonic antigen or carbohydrate antigen 19-9) and poorly differentiated tumor.¹¹ The 5-year survival for all SBC combined together has increased from 33% to 66.9% during the period between 1975 and 2006.¹² With regard to the histopathological types, the 5-year survival is highest for carcinoids (83%) compared with lymphomas, GISTs and adenocarcinomas (62%, 45% and 34%, respectively).^{6,12}

SBC was not comprehensively studied in the South of Egypt, particularly in the heavily populated Sohag governorate. This study is the first, from Sohag University surgical oncology service, to highlight clinical patterns, histopathological varieties, surgical treatment and short and long-term outcome after resection of SBC.

METHODS

A retrospective analysis of medical records of consecutive adult patients with SBC who were admitted at the Department of Surgery, Sohag University Hospital from January 2014 - December 2019 was carried out. The study was conducted in accordance with the guidelines of Sohag University Medical Research Ethics Committee. Eligible patients were >18 years, underwent surgical resection of primary cancerous lesions in the duodenum, jejunum and ileum with histopathological confirmation of SBC. Exclusion criteria were age <18 years, metastatic cancer, peripheral and mediastinal lymphadenopathy, and liver and/or spleen involvement. Data from enrolled patients were demographics and clinical presentation, imaging, endoscopic and laboratory workup, surgical procedures, postoperative complications, histopathological diagnoses and survival rates. Tumor resection was defined according to status of the resection margin as reported by expert pathologist. R0 indicated complete resection, characterized by absence of any residual tumor, either macroscopic or microscopic. Incomplete resection was designated as R1 or R2, indicating presence microscopic or macroscopic residual tumor at the resection margin, respectively). GISTs were classified according to their "risk of aggressive behavior", which considers tumor size and mitotic activity.^{13,14} GISTs with very low risk are those with size <2 cm and mitotic count <5/50 per high power field (HPF); low risk tumors have size of 2-5 cm and mitotic count <5/50 per HPF; intermediate risk describes tumors with size < 5 cm and mitotic count 6-10/50 HPF or size 5-10 cm with mitotic count <5/50 HPF whereas high risk tumors are those with size >5 cm and mitotic count >5/50 HPF or size >10 cm and any mitotic count or mitotic count >10/50 HPF with any tumor size.¹⁴ In patients with established diagnosis of lymphoma, further workup entailed bone marrow aspiration and/or biopsy and immunophenotyping to precisely elucidate tumor cell lineage. Staging was carried out according to modified Ann Arbor criteria (Lugano).¹⁵ In cases of

adenocarcinoma, the depth of invasion of bowel layers, applied for tumor staging according to the American joint committee against cancer. Adenocarcinoma staging was as follows: stage I refers to invasion of the lamina propria, submucosa or muscularis propria without metastases; stage II designates serosal and/or peritoneal invasion; stage III denotes regional lymph node metastases whereas stage IV includes cases with distant metastases.¹¹ Based on careful review of surgical and histopathological data, a multidisciplinary team appropriately decided on the lines of adjuvant therapy whenever indicated. Standard follow-up in the outpatient clinics of surgery and medical oncology was regularly planned every 3 months during the first year and each 6 months thereafter.

RESULTS

Demographics, clinical presentation and histopathological data

Twenty-one patients were enrolled with median age of 62 (range 32-83) years. The majority were males (14, 67%) versus 7 females (33%). The prevailing symptom was abdominal pain that was recorded in all patients. Other presentations included anorexia (15, 71%), fatigue (12, 57%), vomiting (6, 29%), and weight loss (5, 24%). The jejunum was the most common site of tumors (8 patients, 38%), followed by the ileum (7 patients, 33%), and duodenum (6 patients, 29%) (Table 1). GIST was the most common histopathologic type, confirmed in 9 patients. Lymphoma was diagnosed in 8 patients and adenocarcinoma in 4 (Table 2). Emergency presentation occurred in 13 patients (62%) in whom there was failure of diagnosis for variable periods (median: 4, range: 2-11 weeks), including 7 with small bowel obstruction, 5 with acute abdomen and 1 with peritonitis (Table 3). The diagnosis of small bowel mass, wall thickening and/or luminal narrowing was established preoperatively in 13 patients (62%) by abdominal computed tomography (CT) (9, 43%) and upper gastrointestinal endoscopy (4, 19%) (Table 4). During follow-up (median: 16, range: 5-48 months), survival rate was 76% (16 patients alive) while 5 patients died.

Table 1: Demographics, clinical and anatomical data.

Demographic data	Number	(%)
Gender		
Male	14/21	67
Female	7/21	33
Emergency presentations		
Small bowel obstruction	7/21	33
Acute abdomen	5/21	24
Peritonitis	1/21	5
Tumor location		
Duodenum	6/21	29
Jejunum	8/21	38
Ileum	7/21	33

Table 2: Tumor types.

Tumor type	Number	%
GIST	9/21	43
Lymphoma	8/21	38
Adenocarcinoma	4/21	19

GISTs

There were 9 patients with GISTs located in the duodenum (2), jejunum (5) and ileum (2). Besides vague abdominal pain in all patients, associated symptoms of small bowel obstruction with varying severity were reported in 6 and anorexia in 7 patients. Small bowel mass was confirmed in 4 patients (2 jejunal and 2 duodenal) among 7 patients who underwent abdominal CT examination preoperatively. In 5 patients, the diagnosis was established during exploratory laparotomy. Emergency surgery was carried out due to small bowel obstruction (4), acute abdomen (1) and peritonitis (1). All patients were operated through conventional exploratory laparotomy (Figures 1 and 2). Tumor rupture was not reported in any case. Surgical procedure entailed segmental resection with appropriate safety margin and primary bowel re-anastomosis all patients' jejunal and ileal GISTs. Patients with duodenal GISTs underwent local resection and repair over naso-jejunal feeding tube.

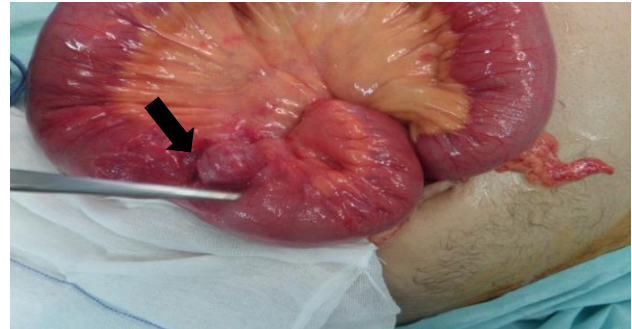


Figure 1: Small bowel intussusception induced by GIST (arrow), pictured after successful reduction.

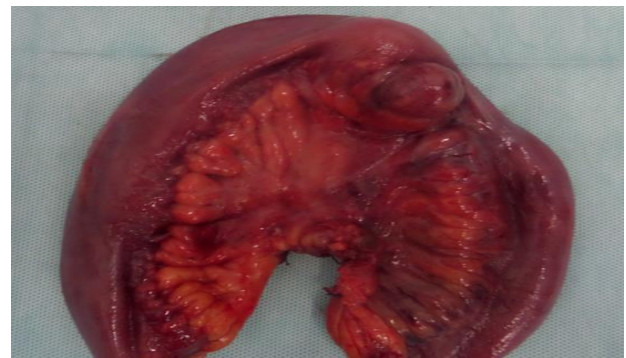


Figure 2: Same tumor (GIST) after resection.

Table 3: Emergency presentation according to tumor type.

	Intestinal obstruction	Acute abdomen	Peritonitis	Total (%)
GIST	4	1	1	6/21 (29)
Lymphoma	3	4	0	7/21 (33)
Adenocarcinoma	0	0	0	0/4 (0)
Total	7/21	5/21	1/21	13/21 (62)

Table 4: Establishment of preoperative diagnosis.

	CT*	Endoscopy**	Total (%)
GIST	4	0	4/21 (29)
Lymphoma	5	0	5/21 (33)
Adenocarcinoma	0	4	4/21 (0)
Total	9/21	4/21	13/21 (62)

*Computed tomography; **Upper gastrointestinal endoscopy

Surgical resection was complete (R0) in 6 patients with jejunal (4) and ileal (2) GISTs. R1 resection was reported in one patient with duodenal and another one with jejunal GISTs. Furthermore, incomplete resection (R2) occurred in one case with duodenal GIST. The risk of aggressive behavior was low in 6 cases, intermediate in 2, and high in only one, details are summarized in Table 5. Five patients received adjuvant targeted therapy (imatinib). Postoperative follow up continued for a median of 18 (range: 8-48) months. One patient with duodenal GIST

with high risk of aggressive behavior and R2 resection died during the eighth month postoperatively. This patient had recurrent duodenal mass and peritoneal secondary deposits.

Another patient with intermediate risk of aggressive behavior developed recurrence 9 months after R1 resection of jejunal tumor with intermediate risk for aggressive behavior. This patient died 18 months after the initial resection.

Lymphoma

Eight patients were diagnosed with small intestinal lymphoma, 5 involved the ileum (4 ileocecal and 1 ileal) and 3 were found in the jejunum. The predominant presentation was non-specific abdominal pain in all patients. Other presentations included anorexia in 6 and intestinal obstruction 3 patients. Among 7 patients who had preoperative CT examination, small bowel wall thickening and luminal narrowing revealed in 5 patients.

Table 5: GISTs, categories according to the risk of aggressive behaviour.

	Duodenal	Jejunal	Ileal	Total (%)
Tumor diameter				
<2 cm	0/2	0/5	0/2	0/9 (0)
2-5 cm	2/2	3/5	2/2	7/9 (78)
6-10 cm	0/2	2/5	0/2	2/9 (22)
>10 cm	0/2	0/5	0/2	0/9 (0)
Mitotic count/50 high power field (HPF)				
<5	1/2	5/5	2/2	6/9 (67)
5-10	0/2	0/5	0/2	2/9 (22)
>10	1/2	0/5	0/2	1/9 (11)
Fletcher classification				
Very low risk	0/2	0/5	0/2	0/9 (0)
Low risk	1/2	3/5	2/2	6/9 (67)
Intermediate risk	0/2	2/5	0/2	2/9 (22)
High risk	1/2	0/5	0/2	1/9 (11)

In 3 cases, small bowel lymphomas (2 ileal and 1 jejunal) were identified during laparotomy. Emergency abdominal exploration was performed for acute abdomen in 4 and acute intestinal obstruction in 3 patients. The predominant histopathological variety was diffuse large B-cell lymphoma (DLBCL). Two patients showed stage I disease, 4 had stage II, while 2 were diagnosed with stage III. Histopathological data and stages shown in Table 6. Complete resection was carried out in 7 patients. Palliative incomplete resection (R2) was performed as debulking procedure of huge tumor. Major postoperative complications occurred in 2 patients. One patient underwent re-laparotomy due to anastomotic leakage. In the second patient, an intra-abdominal abscess required drainage under local anesthesia and ultrasonographic guidance.

Table 6: Lymphoma, histopathological data and stages.

Variables	Number	%
Tumor variety		
Diffuse large B-cell lymphoma	5/8	63
Burkitt's	2/8	25
MALT lymphoma*	1/8	12
Stage		
Stage I	2/8	25
Stage II	4/8	50
Stage III	4/8	25

*MALT=mucosa associated lymphoid tissue

Postoperatively, all patients had adjuvant chemotherapy (CHOP: cyclophosphamide, doxorubicin, oncovin and prednisone) at the department of medical oncology. In 3 cases with positive cluster of differentiation 20 (CD20) antigen, rituximab (a monoclonal antibody) was concomitantly administered with CHOP regimen. During follow-up (median: 26, range: 6-44 months,) 2 patients

died after 7, 23 months. Both patients had stage III disease with signs of progression during the follow-up period.

Adenocarcinoma

In this series, adenocarcinoma was found exclusively in the duodenum in 4 patients. The main presenting symptom was epigastric pain in all patients, vomiting and anorexia in 2 patients. The diagnosis was established preoperatively during upper gastro-intestinal endoscopy and abdominal CT examination.

Pancreatic-duodenectomy was carried out with microscopically and macroscopically free resection margins (R0) for all patients (Figure 3). Stage II diseases was confirmed in 2 patients and stage III in the remaining two. Postoperatively, one patient required re-laparotomy for repair of leaking pancreatico-jejunostomy and peritoneal wash-out and drainage. Otherwise, only minor complications that required no invasive intervention, including mild delayed gastric emptying in two patients and unilateral pleural effusion and wound infection in another patient were recorded.

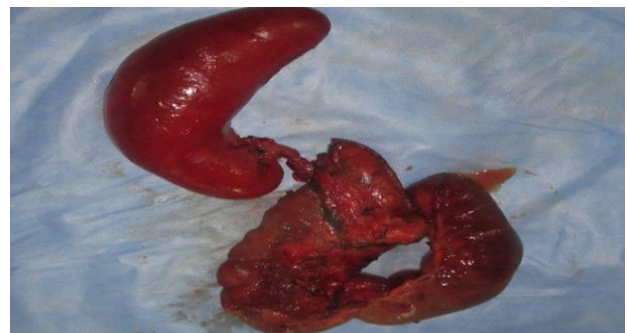


Figure 3: Pancreatico-duodenectomy (Whipple) resected specimen, due to malignant duodenal mass (adenocarcinoma).

Adjuvant chemotherapy with gemcitabine was provided for all 4 cases. Follow-up period ranged from 5 to 28 months. One patient has lost follow-up. Another patient with stage III tumor died due to metastatic disease after 17 months. Two patients had regular follow-up and were alive without recurrence at 15 and 28 months.

DISCUSSION

In this retrospective study, we comprehensively analyzed clinical presentations, anatomical locations, histopathological types, surgical management, complications and survival rates after resection of SBC. This is the first report on this topic from surgical oncology services of Sohag University and the entire Southern part of Egypt.

During the study period of 6 years, 21 consecutive cases with SBC were identified. Despite exclusion of pediatric cases and those with metastasis, the number appears to be small. This is in accordance with the available studies that indicated rarity of SBC.¹⁶

In this study, SBC showed clear predilection toward male gender and older (>60 years) age groups. This is in agreement with previous studies that demonstrated increased incidence of SBC among elderly males.^{2,6,11}

Regarding the predominant histopathologic variety of SBC, the current literature shows conflicting data. For instance, in a comprehensive review on SBC, adenocarcinoma was historically reported as the most common type of SBC, however recent increase in the diagnosis of other types such as GISTs and lymphomas is evident.¹¹ Another study from Lebanon showed almost equal incidence between small bowel adenocarcinoma and lymphoma.¹⁷ Nonetheless, GISTs have been reported to have the highest incidence among other types of SBC.⁶ In our series, GIST was the most common variety of SBC.

Emergency presentations account for around two-thirds of SBC, with intestinal obstruction as the most common cause.^{6,18} Among our patients, 13 (62%) presented as abdominal emergency, with small bowel obstruction as the prevalent diagnosis (7 patients, 54%).

Unlike carcinomas of the gastrointestinal tract, GISTs do not metastasize by the lymphatic route. Therefore, staging systems that rely on spread to lymph nodes are not appropriate for GISTs.¹⁹ Alternatively, the behavior of GISTs was assessed by considering the tumor size and mitotic count.¹⁴ Among our GIST patients, 2 died due to metastasis and recurrent disease during the first 2 years after resection. It should be emphasized that in both patients the resection was not complete. In addition, one case showed high risk and the other exhibited intermediate risk for aggressive behavior. Thus, complete surgical resection and increased risk of aggressive behavior correlated with diminished survival.

The ileum and ileo-cecal region are reported to be the most frequently affected portions of the small bowel with lymphoma.²⁰ In our study, almost two-thirds of cases of lymphoma involved the ileum, among which 80% were located in the ileo-cecal region. In a comprehensive review of SBC, majority of cases were diagnosed with stages I and II at diagnosis.²⁰ Likewise, 75% of patients enrolled in the current study had stage I and II disease.

The ideal approach of management of small bowel lymphoma remains controversial.^{21,22} However, there is strong evidence that initial management with surgical resection followed by adjuvant chemotherapy is associated with increased survival.²¹⁻²³ In our study, this was the standard strategy for management of patients with small bowel lymphoma.

Adenocarcinoma occurs most commonly (almost 15 times higher) in the duodenum compared with the jejunum and ileum.^{2,6} In the same line, among our patients with duodenal cancer, 66% had adenocarcinomas. Interestingly, in this series adenocarcinomas were found exclusively in the duodenum.

In contrast to other types of SBCs which are not accessible through conventional endoscopy diagnosis of duodenal cancer was made preoperatively in all patients during upper gastro-intestinal endoscopy.¹⁸ Thus, all patients with duodenal cancer underwent pancreatico-duodenectomy on elective setting. In agreement with published studies which shows the rate of pancreatic fistula of 25% following pancreatico-duodenectomy, one among 4 patients had postoperative pancreatic fistula which was adequately managed by reoperative surgery.²⁴

It should be emphasized that the current study is limited by the small number of eligible patients and the inherent defects of the retrospective analysis.

CONCLUSION

In conclusion we reported, despite the difficult diagnosis and infrequency of SBC, appropriate surgical procedures and adjuvant therapy are likely to improve the clinical outcome.

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